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INVESTIGATION OF PHYSICO CHEMICAL PROPERTIES AND ENHANCEMENT OF SOLUBILITY OF SALICYLIC ACID BY SUPRAMOLECULAR TECHNIQUE

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ABSTRACT

Supramolecular chemistry is an important interdisciplinary branch of science and compassing ideas of physical and biological process which can be defined as chemistry beyond the molecule' i.e. the chemistry of molecular aggregates assembled via non covalent interactions. The term 'supramolecular synthon' is defined as: "structural units within super molecules which can be formed or assembled by known conceivable synthetic operations involving intermolecular interactions".

INTRODUCTION

In biological processes supramolecular chemistry is nothing but non covalentmolecular binding recognised by Paul Ehlrich and Emil Fisher's lock and key principle through concept of complimentarily and selectively. Progressively non covalent bonds were understood in more detail and the importance of supramolecular chemistry was well established in 1987. Supramolecular chemistry has broad range of applications in different areas such as catalysis, material technology, green chemistry, data storage and processing. Apart from these supramolecular chemistry has been used in the design and development of new pharmaceutical therapies by understanding the interactions at a drug binding site. Although numerous strategies exist for enhancing the bioavailability of drugs with low aqueous solubility.

The success of these approaches is not yet able to be guaranteed and is greatly dependant on the Physical and chemical nature of the molecules being developed. Crystal engineering offers a number of routes to improve solubility and dissolution rate. Which can be adopted through an in-depth knowledge of crystallization processes and the molecular properties of active pharmaceutical ingredients was boiled with 25ml of dil. HCL for 5 minutes filtered and insoluble matter was collected in crucible and washed with hot water and ignited till constant weight. The percentage of acid insoluble ash was calculated with respect to air dried drug.

Co-crystals design: The crystal engineering trails characteristically involves the CSD investigation followed by the experimental

one. Co-crystals design based on the priniciples of supramolecular synthesis; it affords a powerful approach for proactive discovery of novel pharmaceutical solid forms. Co-crystals contains multiple components in given stoichiometric ratio, where different molecular groups interact with hydrogen bonding and by non-hydrogen bonding. The utilization of rules of hydrogen bonding, synthons and graph sets will possibly support in the analysis and design of co-crystal systems. In general at present prediction of whether co-crystallization will occur or not is not yet probable to be replied empirically present. Formation of co-crystal is possibly modernized by consideration of the co-crystallized. Etter and co-workers projected the rules to facilitate the deliberate design of hydrogen-bonded solids.

1. All good proton donors and acceptors are used in hydrogen bonding.
2. Six membered ring intramolecular hydrogen bonds form in preference to inter molecular hydrogen bonds.
3. The best proton donor and acceptor remining after intramolecular hydrogen bonds to one another (but noy all acceptors will necessarily interact with donors).

These observations help to address the issue of competing hydrogen bond assemblies observed when using a particular co-crystallising agent. A comprehensive thoughtful of the supramolecular chemistry of the functional groups present in a given molecule is the qualification for designing the co-crystals as it assists the selection of the appropriate co-crystal former. Supramolecular synthons that can happen in general functional groups so as to design new co-crystals and certain functional groups such as carboxylic acids, alcohols and amides are mainly agreeable to formation of supramolecular heterosynthon the strong hydrogen bond contains(0-H----0), (O-H---N) (-N-H---O), and (-N-H---N). The weak hydrogen bonds involves the -C-H---O and C-H---O=C(72) Co-crystallization of cis-itraconazole with a series of 1,4-dicarboxlic acids accomplished with extended (anti-)conformation were observed. Co-crystals might not be formed from maleic acid with Z regiochemistry about the C=C bond (with pKa=1.9), or form 1,3-or 1,5-dicarboxylic acids. As a result, in this case structural fit emerges to be far more significant than acid-base strength complimentarily for successful co-crystallisation. In the relative humidity stability studies of a series of caffein/carboxylic acid co-crystals. It was established that the oxalic acid which is strongest acid guest molecules produced the caffein co-crystal of most stable, at the same time as the weakest acid (glutaric acid) produced the least stable co-crystal. Though, a polymorph of the glutaric acid/caffeine a co-crystal showed intermediate stability; so pKa alone must not be the only the factor dictating co-crystal stability. The exercise of the hydrogen bonding rules, synthons and graph sets may support in the design and analysis co-crystal system

Co-crystals: Co-crystals are defined as multiple component structures whose components interact by non-covalent interaction such as hydrogen bonding or other weak intermolecular interactions rather than by ion pairing

CO-CRYSTALLISATION METHODS:

- ✓ Solution co-crystallization
- ✓ Mechano chemical co-crystallization

  A) Neat (dry) grinding

  B) Liquid assisted grinding

The application of mechano chemical synthesis for the construction of multi component hydrogen bonded crystals of organo metallic compounds has been extensively studied by braga and co workers. The obsessed increased efficiency of different grinding methodology for co-crystals synthesis over solution based approaches is most likely the result of largely avoiding the effect of solubility and solvent competition they cannot be avoided during solution crystallization

NEAT (DRY) GRINDING: It is useful to identify two different techniques for co-crystal synthesis via grinding. Historically, the first method is neat grinding. Consisting of mixing the co-crystal components components together and grinding them either manually using a motor and pestle, or mechanically using ball mill or vibratory mill.

Mechanisms:

1. Molecular diffusion
2. Eutectic formation
3. Co-crystallization mediated by an amorphous phase

Common to all three distinct mechanisms is that the intermediate bulk phase (a gas, a liquid, or an amorphous solid) should exhibit enhanced mobility and or higher energy of reactant molecules with respect to their starting crystalline forms

LIQUID ASSISTED (KNEADING) GRINDING:

The reactant addition to the tool box of solid state supra molecular synthesis is liquid assisted grinding. In liquid assisted grinding procedure; a small (catalytic) amount of an additional liquid Is added to the grinding mixture. In L.A.G reaction the liquid phase template the formation of porous framework and consequently, can remain loosely bound with in the structure of a product. The small amount of liquid has been suggested to have a purely physical role, acting as a lubricant for the reaction and providing a medium to facilitate molecular diffusion. In some cases, the nature of grinding liquid can have a profound effect on the course of mechano chemical co-crystallization. The L.A.G methodology was originally introduced as a means to increase the rate of co-crystal formation in the solid state, although it was soon established that it provided further benefit over neat grinding procedures like higher yield, higher crystallanity of the product, Ability to control polymorph formation, largely scope of reactants and products. Both neat and liquid assisted grinding has been established as highly efficient methods of screening for co crystals, salts, and polymorphic forms of pharmaceutical compounds. The advent of combinatorial chemistry and high throughput screening has resulted in the rapid identification pf mainly highly potent new chemical entities. Coincident with the increased use of these technologies however has been a developing trend toward the identification of lead compounds with good therapeutic importance, but fail to elect their maximum therapeutic effects because of poor aqueous solubility. While these attributes conspire to provide optimized drug-receptor binding characteristics, they also tend to result in poor drug solubility and poor membrane permeability characteristics. As solubility and permeability is considers prerequisites to oral absorption, many of these drugs exhibit poor and variable bio-availability. Such drugs may be recognized by a high dose to solubility ratio and bioavailability is frequently increased by co - administration of food. The oral delivery of such drugs is frequently associated with implications of low bioavailability. To overcome such problems, various formulation strategies are reported in the literature including the use of surfactant, cyclodextrins, solid dispersions, micrinization, permeation enhancers and lipids. The present investigation deals with co-crystals approach utilizing supramolecular technique for the enhancement of solubility of salicylic acid.

UV-VIS spectrum: Salicylic acid: UV-VIS spectrum of salicylic acid in 2% SLS phosphate buffer PH 6.8 was determined and spectrum was shown in graph no.1. it gave a peak at 302nm, the lamda max which is similar to the obtained reference.

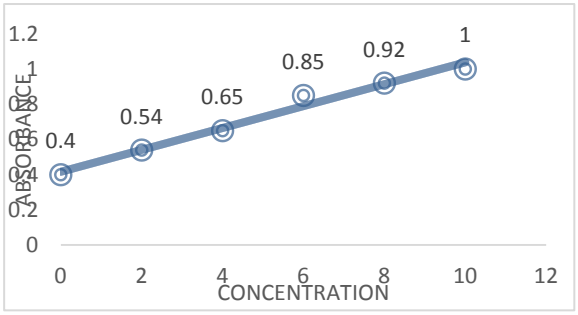
FTIR (Fourier transform infra-red spectroscopy) study of salicylic acid

In FT-IR analysis, the spectrum of pure salicylic acid showed an intense and well-defined bands characteristic to salicylic acid at 3354 1/cm (N-H stretching), 1710 1/cm (c=o stretching), 15391/cm (N02 stretching) 1604 aromatic c=c stretching 1342 cx3 group 861,898 tri substituted benzene 1240 amide C-N, this FTIR Analysis shows that salicylic acid is pure interpretation of IR spectra of salicylic acid has shown fig:

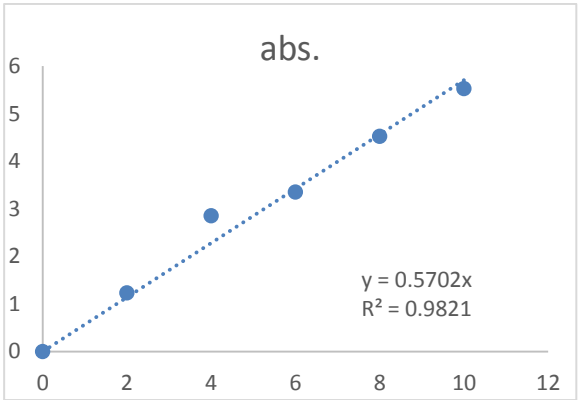
FTIR (Fourier transform infra-red spectroscopy) study of PEG 6000

In FT-IR analysis, the spectrum of pure PEG 6000 showed an intense and well-defined bands characteristic to PEG 6000 at 3641 1/cm (OH-streching vibration), 1669.1 1/cm (C=O stretching), 1622.7 1/cm (Aromatic C=C). this FTIR analysis shows that PEG 6000 is pure. Interpretation of IR spectra of PEG 6000 has shown

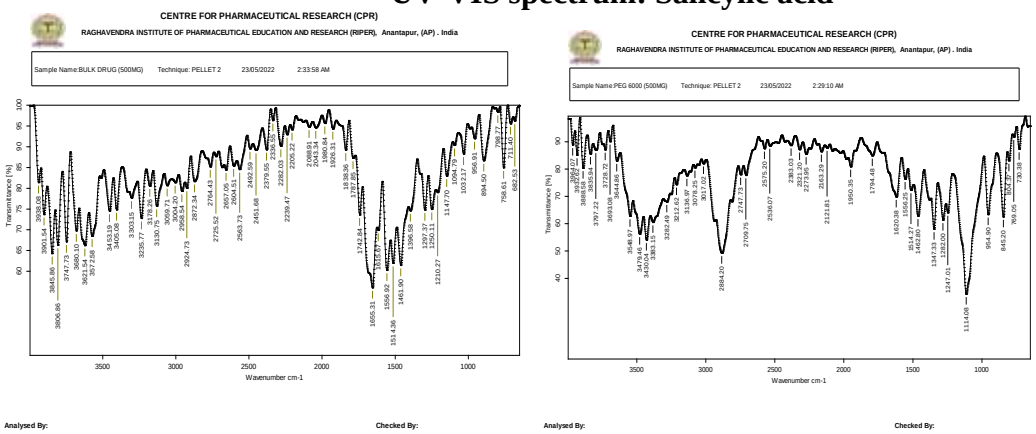
Concentration(µg/ml)	Absorbance
0	0.4
2	0.54
4	0.65
6	0.85
8	0.92
10	1



Concentration(µg/ml)	Absorbance
0	0
2	1.233
4	2.8534
6	3.352
8	4.523
10	5.26



UV-VIS spectrum: Salicylic acid



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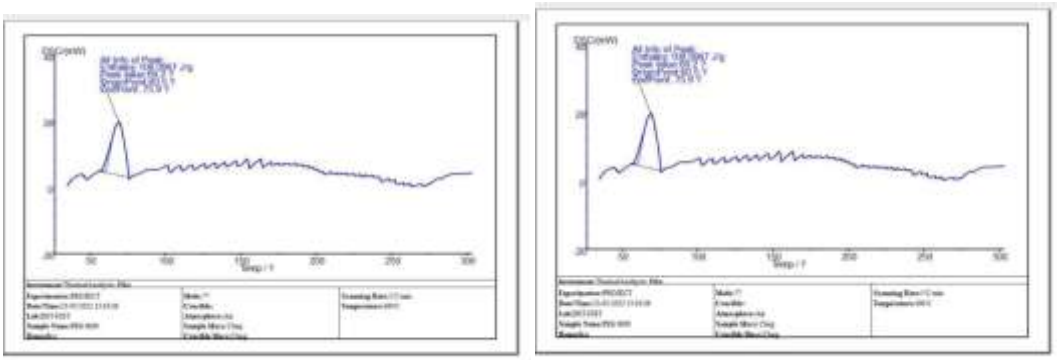
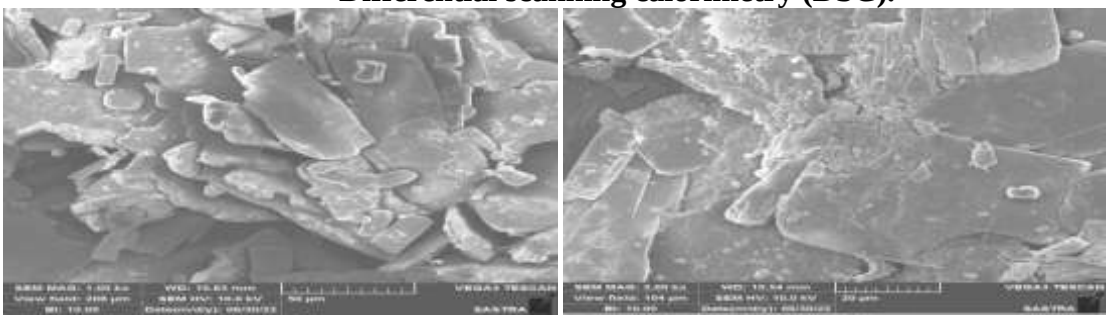
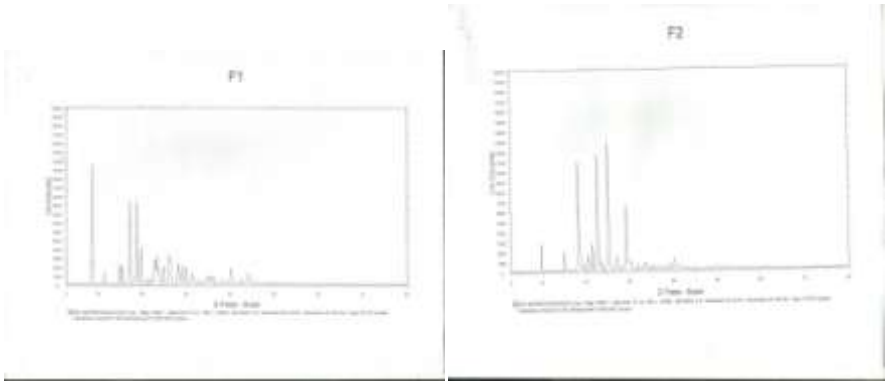
FTIR (Fourier transform infra-red spectroscopy) study



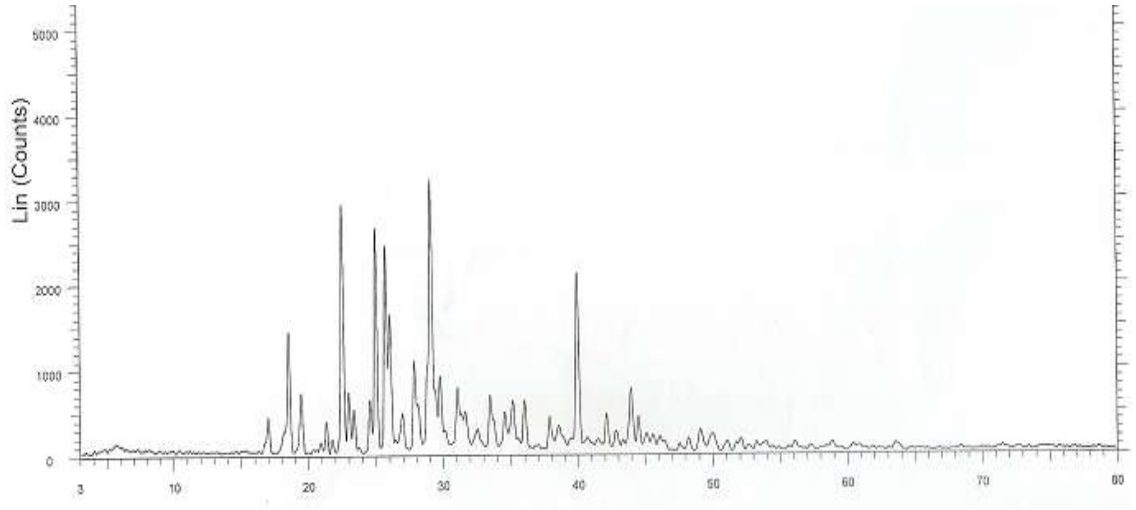
Differential scanning calorimetry (DSC).



Scanning Electron Microscopy (SEM):



X-Ray Powder Diffraction (XRPD)



***In-vitro* dissolution studies:**

TIME(mins)	DISSOLUTION RATE
5	0.4442
15	0.4521
30	0.4625
45	0.4784
60	0.5214

Differential scanning calorimetry (DSC).
Thermal analysis of pure drug, were recorded on a DSC (NETZSCH DSC 204). The temperature axis and cell constant of DSC were previously calibrated with indium. A heating rate of 10 C/min was employed with nitrogen pursing. Powder samples (15-30mg) was weighed into an aluminium pan and analysed as sealed with pin holes and an empty aluminium pan was used as reference.

Scanning Electron Microscopy (SEM): The surface characteristics of Salicylic acid and PEG 600 were studied by SEM (Vegan 3 tescan). The specimens were scanned with an electron beam of acceleration potential of 10 kV and the images were collected as secondary electron mode. X-ray powder diffractometry (XRPD) is a powerful technique for the identification of the crystalline solid phases. Every crystalline solid phase has a unique XRPD pattern, which can form the basis for its identification. The X-ray powder diffraction (XRD) spectra of salicylic acid shows characteristic peak at 25.176^0 (100%), 9.739^0, 15.018^0, 18.28550^0 and 27.084^0 indicates pure salicylic acid.

X-Ray Powder Diffraction (XRPD) study of PEG 6000

X-ray powder diffractometry (XRPD) is a powerful technique for the identification of the crystalline solid phases. Every crystalline solid phase has a unique XRPD pattern, which can form the basis for its identification. The X-ray powder diffraction (XRD) spectra of PEG shows characteristic peak at 25.176^0 (100%), 9.739^0, 15.01^0, 18.850^0, 20.5460 27.0840 29.249^0 and 31.710^0 indicates pure PEG 6000. The X-ray powder diffraction (XRD) spectra of salicylic acid shown characteristic peaks at 25.176^0 (100%), 9.739^0, 15.018^0, 18.28550^0 and 27.084^0. also spectra of PEG 6000 shows characteristic peak at 25.176^0 (100%), 9.739^0, 15.01^0, 18.850^0, 20.5460 27.0840 29.249^0 and $31.710^{0.}$ The X-ray powder diffraction (XRD) spectra of salicylic acid and PEG 6000 co-crystal shows characteristic peak at $29.063^{\ 0}$ which is 100% relative intensity which is different from individual components of salicylic acid and PEG 6000 also at 16.191^0, 24.987^0, 39.928^0 new peaks were appeared. This indicates formation of new crystalline phase.

***IN-VITRO* DISSOLUTION STUDIES:** Dissolution studies of samples weight equivalent to 50 mg were performed using USP XXII apparatus at the stirring speed of 50 rpm and temperature maintained at 37± 0.5◦ C with Phosphate buffer pH6.8 as a dissolution medium. The samples of 5ml were withdrawn at regular intervals of 5, 15,30,45,60 min and filtered. Every time the samples are replaced with 5ml of the fresh dissolution medium. The filtered samples were suitably diluted and analysed for PEG 6000 at 302nm. Percentage drug release from the samples was calculated by using disso software PCP disso V3 software.

ASSAY OF CRYSTALS: 1mg of salicylic acid crystals prepared by solution crystallisation method were taken and dissolved in Phosphate buffer pH6.8. From that 1ml was taken and diluted to 10ml. the absorbance of solution was measured at 431nm using ELICO UV-Visible spectrophotometer and drug content was calculated.

Assay: The assay of salicylic acid was performed the value obtained is 0.0065.

CONCLUSION

This concept was applied to the co-crystallization of salicylic acid with carboxylic acids such as PEG 6000 by solvent evaporation or Solution crystallization method. The carboxylic acid-amide hydrogen bond has again been used to successfully create a new

pharmaceutical co-crystal of salicylic acid, Crystal form with PEG 6000. The supramolecular interaction of Salicylic acid (amide) with carboxylic acid of PEG 6000 resulted in genuine co-crystals. The crystallization of salicylic acid with PEG 6000 is in equal ratio. The prepared co-crystal was characterized in terms of FTIR, SEM and XRD subjected to Preliminary pharmaceutical characterization such as solubility, *In vitro* dissolution studies. From this study it can be concluded that by using supramolecular technique it is possible to enhance the solubility of the poorly soluble drugs.

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